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Design of highly active heterogeneous palladium catalysts for the activation of aryl chlorides in Heck reactions

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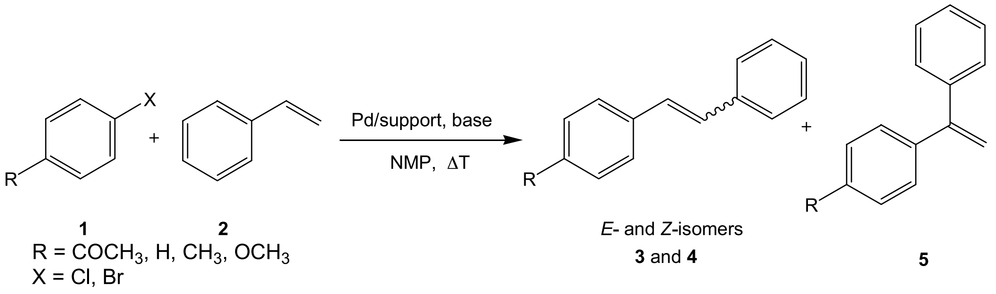
Abstract—In situ generation of highly active palladium species by intermediate dissolution of Pd from solid supported catalysts has been demonstrated to be a very successful approach for the activation of aryl chlorides in Heck reactions. The new 'heterogeneous' Pd catalysts act as reservoir for molecular Pd species with unsaturated coordination sphere in solution. Crucial Pd leaching and re-deposition onto the support can be controlled by optimization of reaction conditions and by the properties of the catalysts. Pd is re-deposited onto the support at the end of the reaction. The catalysts, palladium supported on activated carbon, on various metal oxides or fluorides and Pd complexes in zeolites, are easy to prepare, though the preparation conditions are crucial. The catalysts convert all aryl bromides completely within minutes (TON 100,000). Aryl chlorides (even deactivated ones) are converted with high yields, within 2–6 h. The catalysts belong to the most active ones in Heck reactions at all (including best homogeneous systems) and fulfill all relevant requirements for practical applications in laboratory and industry.

1. Introduction

CC coupling reactions like Heck reactions (Scheme 1) are of growing interest for organic synthesis and fine chemical industry.[1] Advantages of this reaction are a broad availability of aryl bromides and chlorides and the tolerance of a wide variety of functional groups. The Heck reaction is typically catalyzed by Pd complexes in solution. Expensive and often sensitive ligands are necessary to activate Pd and to stabilize it against agglomeration and the formation of Pd black. Accordingly, there have been many efforts to develop new homogeneous systems in the last years.[1]

In addition, several heterogeneous Pd catalysts have been developed in order to overcome typical problems in homogeneous catalysis. The most frequent motivation given is: recovery, recycling, and reuse of the catalyst. However, one of the main and (in our opinion) most important differences between reported homogeneous and heterogeneous systems is the clearly lower activity of the latter catalysts, often being orders of magnitudes lower than that of soluble Pd complexes. This is reflected by the model systems investigated. Typical reports on heterogeneous catalysts focus on aryl iodides and activated aryl bromides as substrates. Reports on the successful activation of



Scheme 1. Heck reaction.

Keywords: CC coupling; Heck reaction; Heterogeneous catalysis; Palladium.

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bromobenzene and in particular of aryl chlorides are very seldom. Most of the reported catalysts that successfully activated aryl chlorides like Pd on activated carbon[2] and layered double hydroxides,[3] Pd complexes bound to polymer matrices[4] or immobilized in porous materials[5] exhibit relevant limitations: they need very long reaction times (several days) or high Pd concentrations for acceptable conversions; restriction on strongly activated aryl chlorides, high selectivity to undesired side products (dehalogenation of the aryl chloride) or a rather complex synthesis of the catalyst itself, which makes it too expensive for possible applications may also be severe problems. Very recently, we have reported that the in situ generation of dissolved Pd species from solid catalysts can be a new and very efficient approach for the activation of aryl chlorides in Heck reactions.[6] Those investigations force of course the discussion on the mechanism of the (heterogeneous) Heck reaction.[7]

While the homogeneous mechanism of the Heck reaction is widely accepted several proposals for the heterogeneous cycle have been made. Several authors suggested a direct interaction between reactants and palladium surface atoms either of supported particles or of colloids in solution as the initial step in the catalytic cycle.[7,8] Shmidt et al.[9] and Arai et al.[10] observed leaching of Pd from the support and claimed these dissolved species to be the active ones. Both performed kinetic investigations on reactions with aryl iodides that indicated a correlation between leaching and reaction rate. In recent years several additional experiments also with non-activated aryl bromides have been reported.[2a,6,7,11] Most of them strongly support this pseudo-homogeneous reaction mechanism and showed that very small amounts of Pd are sufficient for activation of aryl bromides. This interpretation corresponds well with reports of Reetz and de Vries, who achieved similar high activities using 'ligand free' Pd acetate.[12]

With solid catalysts these 'ligand free' active species are generated by dissolution of Pd from the solid. In particular, the determination of the Pd concentration in solution and its correlation with the rate of the Heck reaction were found to be very useful tools for corresponding conclusions.[6,11a] From these observations, the question arose if the control of this leaching process is possible with the aim to speed up the reaction and, which catalyst properties and reaction conditions are the best for the activation of the attractive aryl chlorides by a solid catalyst. This work presents our efforts to elucidate the mechanism of the heterogeneously catalyzed Heck reaction with aryl chlorides. Based on mechanistic insights we optimized heterogeneous Pd catalysts and reaction conditions. As a consequence efficient activation of aryl chlorides became possible by catalysts that are cheap and easily prepared.

2. Results and discussion

2.1. Catalyst preparation

The heterogeneous catalysts presented in this work were specifically prepared to achieve a high dispersion of Pd in oxidation state +II.[11a,13] This has been described and explained to be crucial for high activity and selectivity in Heck reactions of bromobenzene. In order to vary the Pd leaching and re-deposition equilibriums various preparation methods, precipitation of $Pd(OH)_2$ onto different supports, sol-gel techniques and incorporation of Pd(II) complexes into zeolite pores, were used.[14]

2.2. Catalytic activity

The optimized Pd/support catalysts exceed the activity of all heterogeneous catalysts for Heck reactions known so far by at least one order of magnitude. TON of more than 100,000 and TOF up to 39,000 h^{-1} can be achieved with Pd concentrations of less than 0.001 mol% in the Heck reaction of bromobenzene and styrene under standard conditions (NMP, NaOAc, 140 °C, argon atmosphere; Table 1). Comparison of the various support materials did not reveal significant support influences in the reactions. In fact, the high Pd(II) dispersion is found to be crucial also for the present investigations.

Applying exactly the same conditions in the reaction of 4-chloroacetophenone and styrene no conversion is observed. The addition of tetra-*n*-butylammoniumbromide (TBAB) and higher temperature (160 °C) lead to 65% conversion. Addition of TBAB probably prevents Pd agglomeration at this elevated temperature and Br^- can act as a supporting ligand for 'naked' Pd atoms (i.e., the system is now no longer 'ligand free'). Further improvements can be achieved by substitution of the base. While NaOAc leads only to 65% conversion, complete conversion occurs within 2 h using $Ca(OH)_2$ (Fig. 1, Table 2). TON of 10,000–20,000 and TOF of 5000–10,000 h^{-1} are obtained

Table 1. Heck coupling of bromobenzene and styrene

Entry	Catalyst	Catalyst concentration (mol%)	Conversion (%)	Yield **3** (%)	TON[a]	TOF (h^{-1})[b]
1	Pd/TiO_2[c]	0.0011	95	86	87,000	22,000[d]
2	Pd/Al_2O_3[c]	0.0009	96	87	107,000	27,000[d]
3	Pd/TiO_2[c]	0.001	78	71	78,000	39,000
4	Pd/Al_2O_3[e]	0.01	99	94	10,000	5000
5	Pd/AlF_3[c]	0.009	99	93	11,000	5500
6	Pd/MgF_2[c]	0.009	99	93	11,000	5500

Conditions: 10 mmol bromobenzene, 15 mmol styrene, 12 mmol NaOAc, 10 mL NMP, argon atmosphere, 2 h.

[a] Moles of aryl halide converted/moles of Pd.

[b] TON/h.

[c] Prepared by precipitation of $Pd(OH)_2$ on support.

[d] 4 h reaction time.

[e] Prepared by sol–gel method.

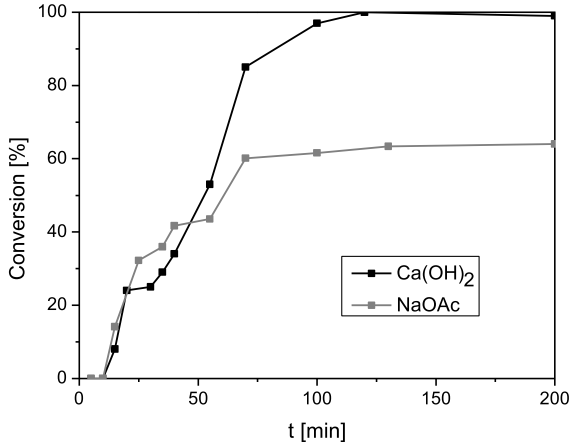

Figure 1. Kinetic investigations: influence of the base on the Heck coupling of 4-chloroacetophenone with styrene. Reaction conditions: 10 mmol 4-chloroacetophenone, 12 mmol styrene, 12 mmol base, 6 mmol TBAB, 10 mL NMP, 0.01 mol% Pd/Al$_2$O$_3$ catalyst, 160 °C.

Table 2. Heck coupling of aryl chlorides and styrene

Entry	Aryl halide	Catalyst	Catalyst concentration (mol%)	Conversion (%)	Yield **3** (%)
1	4-Chloroacetophenone[a]	Pd/Al$_2$O$_3$[b]	0.01	98	90
2	4-Chloroacetophenone[a]	Pd/Al$_2$O$_3$[c]	0.01	87	83
3	4-Chloroacetophenone[a]	Pd/NaY[d]	0.005	99	95
4	Chlorobenzene	Pd/Al$_2$O$_3$[b]	0.1	45	40[e]
5	Chlorobenzene	Pd/AlF$_3$[b]	0.1	36	32[e]
6	Chlorobenzene	Pd/Al$_2$O$_3$[c]	0.1	33	30[e]
7	Chlorobenzene	Pd/C[f]	0.1	33	32[e]
8	Chlorobenzene	Pd/Ce/Al$_2$O$_3$[c]	0.1	54	51[e]
9	Chlorobenzene	Pd/CeO$_2$[b]	0.1	54	51[e]
10	Chlorobenzene	Pd/NaY	0.05	49	45
11	Chlorobenzene	Pd/NaY	0.05	85	83[e]
12	4-Chlorotoluene	Pd/NaY	0.05	40	36[e]
13	4-Chloroanisole	Pd/NaY	0.05	21	19[e]

Conditions: 10 mmol aryl halide, 12 mmol styrene, 12 mmol Ca(OH)$_2$, 6 mmol TBAB, 10 mL NMP, argon atmosphere, 6 h.

[a] 2 h reaction time.

[b] Prepared by precipitation of Pd(OH)$_2$ on support.

[c] Prepared by sol–gel method.

[d] Without TBAB.

[e] O$_2$ atmosphere.

[f] E105 CA/W, Degussa AG.

with different catalysts. In the case of Pd/NaY addition of TBAB can be even renounced.

Kinetic investigations showed that the concentration of the molecular Pd species in solution correlates with the reaction course (Fig. 2). The highly active Pd species are generated in situ. Pd is dissolved from the support, stabilized against agglomeration by dissolution-re-precipitation equilibriums with the surface and re-deposited onto the support at the end of the reaction (after consumption of the aryl chloride).

The conversion of non-activated aryl chlorides like chlorobenzene occurs only satisfactorily if TBAB is added (independent of the support). The best results were achieved with Pd incorporated into the cages of a zeolite (Pd/NaY). Using this catalyst 85% conversion and a yield of 83% of *E*-stilbene were obtained in the Heck reaction of chlorobenzene and styrene within 6 h (TON = 1400, Table 2). This system is particularly suitable to avoid agglomeration of Pd probably by diffusion control. Good results could also be achieved with different other supports, if specific redox conditions were adjusted in the system (Table 2, entries 4–9). Pd re-oxidation by oxygen and/or the support plays a crucial role too. In oxygen atmosphere higher yields could be achieved than in argon atmosphere (Table 2, entries 10, 11). This may be explained by partial re-oxidation of Pd to Pd(II) (lower concentration of Pd(0)) thus preventing Pd agglomeration (Pd black formation).

The use of Pd/NaY and a careful choice of reaction parameters allow the activation and conversion even of deactivated aryl chlorides, like 4-chlorotoluene and 4-chloroanisole, in Heck reactions (Table 2, entries 12, 13). Note, that the selectivity to the Heck products is 100% in all cases and that the problematic dehalogenation which is often found for reactions of aryl chlorides did not occur. We explain this by the controlled prevention of Pd particle formation in the present system (assuming that dehalogenation occurs according to a truly heterogeneous surface mechanism).

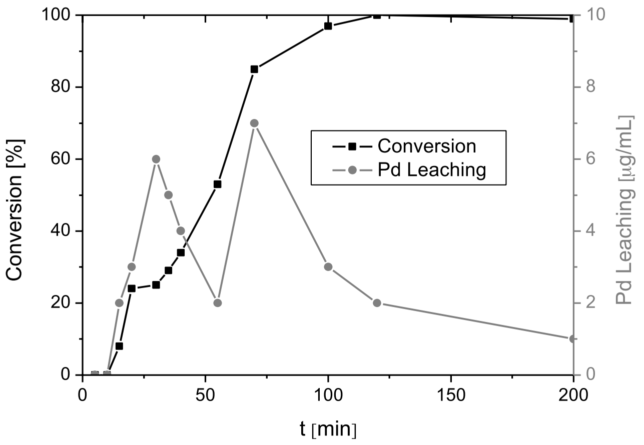

Figure 2. Kinetic investigations and Pd leaching: Heck coupling of 4-chloroacetophenone with styrene. Reaction conditions: 10 mmol 4-chloroacetophenone, 12 mmol styrene, 12 mmol Ca(OH)$_2$, 6 mmol TBAB, 10 mL NMP, 0.01 mol% Pd/Al$_2$O$_3$ catalyst, 160 °C.

2.3. Pd leaching as a function of reaction time

The progress of the reaction and the Pd content in solution were monitored for different substrates (4-chloroacetophenone, chlorobenzene) and catalysts (Pd/Al_2O_3, Pd/NaY zeolite, Figs. 2 and 3). In all cases the active Pd species are generated by dissolution from the support. They are stabilized against agglomeration by dissolution-re-precipitation equilibriums with the surface and re-deposited onto the support at the end of the reaction. For chlorobenzene and Pd/NaY zeolite catalysts Pd is dissolved (concentration reaches maximum after 20 min) and the conversion of chlorobenzene starts. The Pd content in solution decreases with the degree of aryl chloride consumed. The Pd concentrations in solution and the course of the reaction depend on catalyst, substrate, temperature, base, solvent, and additives. The maximum absolute amount of Pd in solution is higher for the optimized reaction system and chlorobenzene compared to 4-chloroacetophenone. Obviously the lower concentration in the latter case (controlled by the chosen reaction parameters) is not sufficient to activate the less reactive chlorobenzene. Even small divergences of the Pd content in solution correlated with fluctuations in the reaction course (Fig. 3). The divergences of the Pd concentration in solution may be due to the experimental procedure (disturbances/interruptions by the withdrawal of samples from the reaction mixture) or due to differences in the single reaction vessels (see Section 4). Note, that also the zeolite system shows leaching of Pd into bulk solution during the reaction. Obviously, the reaction takes place outside the zeolite pores. Pd leaves the pore system, catalyzes the Heck reaction and diffuses back into the pores (equilibrium).

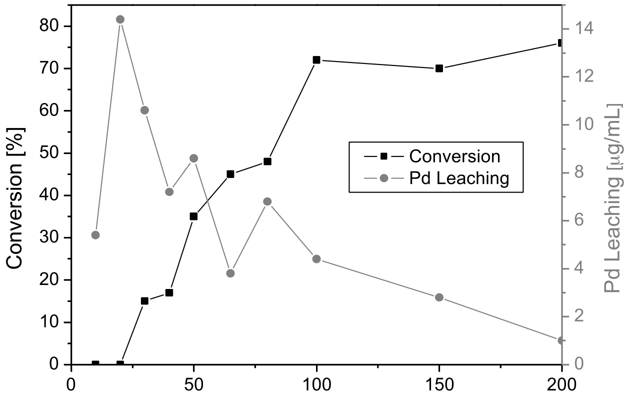

Figure 3. Kinetic investigations and Pd leaching: Heck coupling of chlorobenzene with styrene. Reaction conditions: 10 mmol chlorobenzene, 12 mmol styrene, 12 mmol $Ca(OH)_2$, 6 mmol TBAB, 10 mL NMP, 0.05 mol% Pd/NaY catalyst, 160 °C, O_2 atmosphere.

2.4. Catalyst recycling and reuse

The catalysts were recyclable several times. This is illustrated by the reaction of bromobenzene and styrene. Only a slight decrease in activity emerges in the second run (86% conversion). In the third run, still 69% conversion is achieved (Table 3). The decrease is caused by a partial reduction of Pd(II) to Pd(0) and a lower Pd dispersion after re-deposition. In contrast to observations with activated aryl bromides made by de Vries et al.,[15] reactivation of the catalyst by I_2 or Br_2 was not possible.

Table 3. Heck coupling of bromobenzene and styrene–catalyst recycling experiments

Entry	Run	Conversion (%)	Yield **3** (%)
1	1	98	90
2	2	86	80
3	3	69	62

Conditions: 10 mmol bromobenzene, 15 mmol styrene, 12 mmol NaOAc, 10 mL NMP, argon atmosphere, 140 °C, 6 h, 0.2 mol% Pd/Al_2O_3.

3. Conclusions

Pd supported on various oxides, fluorides and activated carbon and incorporated into zeolites can be an extremely active and selective catalyst for Heck reactions. The catalytic systems combine extremely high activity, short reaction times, and high selectivity in Heck reactions of aryl bromides and chlorides with the advantages of easy and complete Pd separation and recovery. The activity is comparable to the very best homogeneous catalyst systems. The heterogeneous catalysts are stable against air and moisture, no inert atmosphere and no expensive ligands are necessary. They are easy to prepare, the preparation conditions are crucial (high dispersion and +II oxidation state of Pd, certain water content, no thermal treatment or pre-reduction). Pd complexes ($[Pd(NH_3)_4]^{2+}$) incorporated into the pore system of zeolites (NaY) represent the best catalytic performances. Side reactions (dehalogenation) and Pd black formation can be excluded.

The development of these simple catalysts was possible by enlightenment of the reaction mechanism and corresponding careful optimization as well as choice of reaction parameters and catalyst properties. The highly active Pd species are generated in situ by intermediate dissolution of Pd from the solid support. The 'heterogeneous' Pd catalysts act as a reservoir for coordinative unsaturated molecular Pd species in solution. Pd is re-deposited onto the support at the end of the reaction. These processes are crucial and immanent components of the catalytic cycle, which obviously also involves heterogeneous reactions (oxidative addition of aryl halide to surface palladium atoms initializing dissolution). The Pd amount in solution correlates with the reaction rate and is strongly influenced by the reaction conditions. Solvent, temperature, substrates, base, additives, and atmosphere must be adjusted carefully. Experiments monitoring the Pd concentration in solution as a function of reaction rate were the most valuable tools for corresponding mechanistic studies. Pd leaching is a precondition for high activity and selectivity of heterogeneous catalysts in Heck reactions.

4. Experimental

4.1. General procedure for catalysis experiments

Reactions were performed in sealed pressure tubes after 5 min of purging with argon. Educts and solvents were used non-dried.

Filtered samples were extracted with water/CH_2Cl_2 and dried over $MgSO_4$. Products were identified by GC/MS. Conversions and yields were quantified by GLC using diethylene glycol dibutylether as internal standard ($\Delta_{rel} = \pm 5\%$).

4.2. Typical reaction conditions for Heck reactions with bromobenzene

10 mmol bromobenzene, 15 mmol styrene, 12 mmol NaOAc, about 0.001 mol% Pd/support, 10 mL NMP (1-methyl-2-pyrrolidone), $T = 140$ °C, 2–4 h.

4.3. Typical reaction conditions for Heck reactions with aryl chlorides

10 mmol aryl chloride, 12 mmol styrene, 12 mmol $Ca(OH)_2$, 0.01–0.1 mol% Pd/support, 10 mL NMP, $T = 160$ °C, 2–6 h.

4.4. Typical reaction procedure for kinetic investigations

Sixteen identical experiments were performed in 16 pressure tubes as described above. At defined times the reactions were quenched. For Pd leaching 5 mL of the filtered sample were evaporated. Pd content of the residue was analyzed by flame AAS.

4.5. Recycling experiments

10 mmol bromobenzene, 15 mmol styrene, 12 mmol NaOAc, 0.2 mol% Pd/Al_2O_3, 10 mL NMP, $T = 140$ °C, $t = 6$ h. After the reaction was finished, the catalyst was washed three times with CH_2Cl_2 and re-used.

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References and notes

1. Beletskaya, I. P.; Cheprakov, A. V. *Chem. Rev.* **2000**, *100*, 3009–3066.
2. (a) Zhao, F.; Arai, M. *React. Kinet. Catal. Lett.* **2004**, *81*, 281–289. (b) Mukhopadhyay, S.; Rothenberg, G.; Joshi, A.; Baidossi, M.; Sasson, Y. *Adv. Synth. Catal.* **2002**, *344*, 348–354.
3. Choudary, B. M.; Madhi, S.; Chowdari, N. S.; Kantam, M. L.; Sreedhar, B. *J. Am. Chem. Soc.* **2002**, *124*, 14127–14136.
4. (a) Buchmeiser, M. R.; Wurst, K. *J. Am. Chem. Soc.* **1999**, *121*, 11101–11107. (b) Buchmeiser, M. R.; Schareina, T.; Kempe, R.; Wurst, K. *J. Organomet. Chem.* **2001**, *634*, 39–46. (c) Silberg, J.; Schareina, T.; Kempe, R.; Wurst, K.; Buchmeiser, M. R. *J. Organomet. Chem.* **2001**, *622*, 6–18. (d) Ley, S. V.; Ramarao, C.; Gordon, R. S.; Holmes, A. B.; Morrison, A. J.; McConvey, I. F.; Shirley, I. M.; Smith, S. C.; Smith, M. D. *J. Chem. Soc., Chem. Commun.* **2002**, 1134–1135.
5. (a) Mehnert, C. P.; Ying, J. Y. *J. Chem. Soc., Chem. Commun.* **1997**, 2215–2216. (b) Mehnert, C. P.; Weaver, D. W.; Ying, J. Y. *J. Am. Chem. Soc.* **1998**, *120*, 12289–12296. (c) Djakovitch, L.; Köhler, K. *J. Am. Chem. Soc.* **2001**, *123*, 5990–5999. (d) Srivastava, R.; Venkatathri, N.; Srinivas, D.; Ratnasamy, P. *Tetrahedron Lett.* **2003**, *44*, 3649–3651.
6. Pröckl, S. S.; Kleist, W.; Gruber, M. A.; Köhler, K. *Angew. Chem., Int. Ed.* **2004**, *43*, 1881–1882.
7. Biffis, A.; Zecca, M.; Basato, M. *J. Mol. Catal. A: Chem.* **2001**, *173*, 249–274.
8. (a) Kaneda, K.; Higuchi, M.; Imanaka, T. *J. Mol. Catal.* **1990**, *63*, L33–L36. (b) LeBlond, C. R.; Andrews, A. T.; Sun, Y.; Sowa, J. R. *Org. Lett.* **2001**, *3*, 1555–1557. (c) Reetz, M. T.; Westermann, E. *Angew. Chem.* **2000**, *112*, 165–168.
9. Shmidt, A. F.; Mametova, L. V. *Kinet. Catal.* **1996**, *37*, 406–408.
10. Zhao, F.; Murakami, K.; Shirai, M.; Arai, M. *J. Catal.* **2000**, *194*, 479–483.
11. (a) Köhler, K.; Heidenreich, R. G.; Krauter, J. G. E.; Pietsch, J. *Chem. Eur. J.* **2002**, *8*, 622–631. (b) Schmidt, A. F.; Smirnov, V. V. *J. Mol. Catal. A: Chem.* **2003**, *203*, 75–78.
12. (a) Reetz, M. T.; Westermann, E.; Lohmer, R.; Lohmer, G. *Tetrahedron Lett.* **1998**, *39*, 8449–8452. (b) de Vries, A. H. M.; Mulders, J. M. C. A.; Mommers, J. H. M.; Henderickx, H. J. W.; de Vries, J. G. *Org. Lett.* **2003**, *5*, 3285–3288. (c) Reetz, M. T.; de Vries, J. G. *Chem. Commun.* **2004**, 1559–1563.
13. (a) Heidenreich, R. G.; Krauter, J. G. E.; Pietsch, J.; Köhler, K. *J. Mol. Catal. A: Chem.* **2002**, *182–183*, 499–509. (b) Heidenreich, R. G.; Köhler, K.; Krauter, J. G. E.; Pietsch, J. *Synlett* **2002**, *7*, 1118–1122.
14. (a) Pearlman, W. *Tetrahedron Lett.* **1967**, *17*, 1663–1664. (b) Djakovitch, L.; Heise, H.; Köhler, K. *J. Organomet. Chem.* **1999**, *584*, 16–26. (c) Fessi, S.; Ghorbel, A. *J. Sol-Gel Sci. Technol.* **2000**, *19*, 417–420.
15. de Vries, A. H. M.; Parlevliet, F. J.; Schmieder-van de Vondervoort, L.; Mommers, J. H. M.; Henderickx, H. J. W.; Walet, M. A. M.; de Vries, J. G. *Adv. Synth. Catal.* **2002**, *344*, 996–1002.